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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	27

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/444,284	Applicant(s) Vogels et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 28, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2, 19, 21, 25, 28-32, 37-40, 42, and 44-71* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2, 19, 21, 25, 28-32, 37-40, 42, and 44-71* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 24
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-28-03 has been entered.

Applicants' amendment and Dr. Jaap Goudsmit's declaration filed 4-28-03 have been entered. Claims 1, 4-18, 20, 24, 26, 41 and 43 have been canceled. Claims 2, 19, 21, 25, 37-40, 42 and 44-58 have been amended. Claims 59-71 have been added. Claims 2, 19, 21, 25, 28-32, 37-40, 42 and 44-71 are pending and under consideration.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the nucleotide sequence or amino acid sequence on Figures 4A-4E and Figures 9A and 9B do not have sequence identifier either on the figures or "Brief Description of Drawings". If any of the nucleotide sequences and amino acid sequences is not on the already submitted sequence listing, Applicants must provide a substitute CRF copy of the sequence listing, a substitute paper copy of sequence listing, and a statement indicating the content of the paper and CRF copies are the

same, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 51-54, 56, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "adenoviral nucleic acid incorporated within said recombinant virus capsid" in claim 51 is vague and renders the claim indefinite. It is unclear how an adenoviral nucleic acid can be incorporated within said recombinant virus capsid. Is the adenoviral nucleic acid covalently or non-covalently attached to the virus capsid or said adenoviral nucleic acid is integrated into the recombinant adenovirus genome or... Claims 52-54 depend on claim 51 but fail to clarify the indefiniteness.

The phrase "non-adenoviral nucleic acid incorporated into said recombinant virus capsid" in claim 56 is vague and renders the claim indefinite. It is unclear how a non-adenoviral nucleic acid can be incorporated into said recombinant virus capsid. Is the non-adenoviral nucleic acid covalently or non-covalently attached to the virus capsid or said non-adenoviral nucleic acid is

integrated into the recombinant adenovirus genome or... Claim 57 depends on claim 56 but fail to clarify the indefiniteness.

3. Claims 2, 21, 25, 38-40, 42, 60-65 and 69-71 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "with a reduced tissue tropism for liver cells" in claims 2 and 25 is vague and renders the claim indefinite. It is unclear what is compared to such that "reduced tropism for liver cells" is determined. Claims 21, 38-40 and 42 depend on claim 2 but fail to clarify the indefiniteness. Changing "with a reduced tissue tropism for liver cells" to "with a reduced tissue tropism for liver cells as compared to the corresponding wild type adenovirus" would be remedial.

The phrase "with a reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells" in claim 60 is vague and renders the claim indefinite. It is unclear what is compared to such that "reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells" is determined. Claims 61-65 depend on claim 60 but fail to clarify the indefiniteness. Changing "with a reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells" to "with a reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells as compared to the corresponding wild type adenovirus" would be remedial.

The phrase "having a reduced tropism for liver cells" in claim 69 is vague and renders the claim indefinite. It is unclear what is compared to such that "reduced tropism for liver cells" is determined. Claims 70 and 71 depend on claim 69 but fail to clarify the indefiniteness. Changing "having a reduced tropism for liver cells" to "having a reduced tropism for liver cells as compared to the corresponding wild type adenovirus" would be remedial.

4. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps are: what is compared to so as to determine the tropism of an adenovirus capsid for liver cells is reduced.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 21, 25, 38-40, 42, 44-65 and 69-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on a recombinant adenovirus with a reduced tropism for liver cells, an adenovirus capsid with a reduced tissue tropism for liver cells comprising proteins from at least

two different adenoviruses and at least one protein includes at least a tissue tropism determining fragment of a fiber protein of subgroup B adenovirus, a recombinant adenovirus comprising a recombinant virus capsid having protein fragments from at least two different viruses and said recombinant virus capsid has an increased tropism for endothelial cells when compared to other adenovirus capsids, or the recombinant adenovirus further comprises an adenoviral or non-adenoviral nucleic acid incorporated into said recombinant virus capsid, a pharmaceutical composition comprising the recombinant adenovirus of claim 2, and a recombinant adenovirus having a capsid with a reduced tropism for liver cells and an increased tropism for smooth muscle cells (SMC) and endothelial cells, wherein said recombinant adenovirus comprises a chimeric fiber protein comprising at least the knob domain of a fiber protein of adenovirus type 16 and the remaining part of the fiber protein is of a different adenovirus serotype.

The specification discloses the generation of recombinant adenovirus chimeric for fiber protein of adenovirus type 11, 12, 16, 28, 35, 40 and 51 and shows that fiber chimera 12 and 28 are unable to infect HUVEC endothelial cells or smooth muscle cells, the 40L infect those cells with similar efficiency as control Ad5 virus, and adenovirus fiber 16 chimera infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 (specification, bridging page 38-39, and 41). The claims encompass any recombinant adenovirus having various capsid proteins or fiber proteins from **any virus**, including **any adenovirus** and **any non-adenovirus**, and said recombinant adenovirus has at least a tissue tropism for smooth muscle cells or increased tropism for endothelial cells, or with a reduced

tissue tropism for liver cells, and the tropism could be provided by a virus capsid comprising protein **fragments** from at least two different viruses.

The scope of the claim includes nucleic acid vectors or viruses encoding a genus of numerous structural variants of the tropism-determining protein, such as fiber protein of adenovirus, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The claims (especially, claims 2, 25, 37, 44, 60, 66 and 69) read on recombinant virus having reduced tropism for liver cells, or increased tropism for endothelial cell or smooth muscle cells as compared to any other adenovirus capsid or any virus. Since each adenovirus or virus likely has different degree of tropism for liver cells, endothelial cells and smooth muscle cells, the claimed recombinant adenoviruses, cells and adenovirus capsids depend on what adenovirus or virus is used for comparison. Thus, the claims encompass very broad genus of numerous structural variants of the tropism-determining protein derived from various adenoviruses or other viruses. The specification fails to provide the structural features of a tropism-determining protein from different viruses, including adenoviruses and non-adenoviruses. No structural feature of the viral fiber or capsid protein that contributes to increased tropism for smooth muscle cells or endothelial cells, or a reduced tissue tropism for liver cells has been disclosed. Structural features that could distinguish compounds in the genus from others in the polypeptide class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is

needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the fiber protein chimeras as disclosed in the present application is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed recombinant adenovirus. Thus, it is concluded that the written description requirement is not satisfied for the genus of proteins or recombinant adenovirus encoding or carrying said proteins as claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the nucleic acid vectors or adenovirus encoding the disclosed fiber protein chimeras, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants argue that the claims have been amended to read on recombinant adenovirus and the specification provides support for the recombinant adenovirus with reduced tissue tropism for liver cells and increased tropism for endothelial cells (amendment, p. 12). This is not found persuasive because of the reasons set forth above.

7. Claims 2, 19, 21, 25, 28-32, 37-40, 42 and 44-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adenovirus fiber 16 chimera that infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 *in vitro* and none of the disclosed fiber chimeras are targeted specifically to liver and spleen *in vivo*, does not reasonably provide enablement for any recombinant adenovirus with a reduced tropism for liver cells, any adenovirus capsid with a reduced tissue tropism for

liver cells comprising proteins from at least two different adenoviruses and at least one protein includes at least a tissue tropism determining fragment of a fiber protein of subgroup B adenovirus, any recombinant adenovirus comprising a recombinant virus capsid having protein fragments from at least two different viruses and said recombinant virus capsid has an increased tropism for endothelial cells when compared to other adenovirus capsids, a pharmaceutical composition comprising the recombinant adenovirus of claim 2, cells for producing a recombinant adenovirus having tissue tropism for smooth muscle cells by using at least one adenoviral nucleic acid encoding a subgroup B fiber protein, and any recombinant adenovirus having a capsid with a reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells, wherein said recombinant adenovirus comprises a chimeric fiber protein comprising at least the knob domain of a fiber protein of adenovirus type 16 and the remaining part of the fiber protein is of a different adenovirus serotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a recombinant adenovirus with a reduced tropism for liver cells, an adenovirus capsid with a reduced tissue tropism for liver cells comprising proteins from at least two different adenoviruses and at least one protein includes at least a tissue tropism determining fragment of a fiber protein of subgroup B adenovirus, a recombinant adenovirus comprising a recombinant virus capsid having protein fragments from at least two different viruses and said recombinant virus capsid has an increased tropism for endothelial cells when

compared to other adenovirus capsids, or the recombinant adenovirus further comprises an adenoviral or non-adenoviral nucleic acid incorporated into said recombinant virus capsid, a pharmaceutical composition comprising the recombinant adenovirus of claim 2, and a recombinant adenovirus having a capsid with a reduced tropism for liver cells and an increased tropism for smooth muscle cells and endothelial cells, wherein said recombinant adenovirus comprises a chimeric fiber protein comprising at least the knob domain of a fiber protein of adenovirus type 16 and the remaining part of the fiber protein is of a different adenovirus serotype.

The specification discloses the generation of recombinant adenovirus chimeric for fiber protein of adenovirus type 11, 12, 16, 28, 35, 40 and 51 and shows that fiber chimera 12 and 28 are unable to infect HUVEC endothelial cells or smooth muscle cells, the 40L infect those cells with similar efficiency as control Ad5 virus, and adenovirus fiber 16 chimera infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 (specification, bridging page 38-39, and 41). The claims encompass any recombinant adenovirus having various capsid proteins or fiber proteins from any virus, including **any adenovirus** and **any non-adenovirus**, and said recombinant adenovirus has at least a tissue tropism for smooth muscle cells or increased tropism for endothelial cells, or with a reduced tissue tropism for liver cells, and the tropism could be provided by a virus capsid comprising protein **fragments** from at least two different viruses. The claims (especially, claims 2, 25, 37, 44, 60, 66 and 69) read on recombinant virus having reduced tropism for liver cells, or increased

tropism for endothelial cell or smooth muscle cells as compared to any other adenovirus capsid or any virus. Since each adenovirus or virus likely has different degree of tropism for liver cells, endothelial cells and smooth muscle cells, the claimed recombinant adenoviruses, cells and adenovirus capsids depend on what adenovirus or virus is used for comparison. Thus, the claims encompass very broad genus of numerous structural variants of the tropism-determining protein derived from various adenoviruses or other viruses.

The specification fails to provide adequate guidance and evidence for how to alter the tropism-determining protein of an adenovirus, a non-adenovirus, or a non-virus such that the mutated protein or chimeric protein fragments from various adenovirus serotypes or other viruses or from at least two different viruses could provide tissue tropism for smooth muscle cells, increased tropism for endothelial cells or provide reduced tissue tropism for liver cells *in vitro* or *in vivo*. The claims encompass various adenoviruses and non-adenoviruses, such as retroviruses, derived from various organisms. "At present, six different subgroups of human adenoviruses have been proposed which in total encompass approximately 50 distinct adenovirus serotypes. Besides these human adenoviruses, many animal adenoviruses have been identified" (Specification, page 4). "These serotypes differ in at least capsid proteins (penton-base, hexon), proteins responsible for cell binding (fiber protein), and proteins involved in adenovirus replication. It is unknown to what extent the capsid proteins determine the difference in tropism found between the serotypes. It may well be that post-infection mechanisms determine cell type specificity of adenoviruses" (specification, page 5). Subgroup B1 of adenovirus includes

serotype 3, 7, 16, 21 and 51, and subgroup B2 includes 11, 14, 34 and 35. The specification of the present application states that "efficient infection of SMC is not a general trade of all subgroup B fiber molecules. Clearly fiber 16 and fiber 11 are better suited for infection of SMC than fiber 35 and fiber 51" (page 42). Further, Mei et al., 1998 (Virology, Vol. 240, p. 254-266, IDS) shows that two closely related adenovirus Ad11p and Ad11a, which have kidney or respiratory tract tropism, differ in their binding to epithelial cells of various origin. Mei reports that "the cell susceptibility of Ad11p and Ad11a infection strongly depends on both the number of fiber receptors on the host cells and the receptor affinity for ligands on the fiber knob. Our findings also suggest that the receptors for Ad11p and Ad11a on the surface of different cell types may be different or on different sites" (e.g. abstract). Therefore, it would be unpredictable at the time of the invention whether an adenovirus serotype or other viruses can infect or have tropism for a particular cell type, including liver cells, endothelial cells and smooth muscle cells, *in vitro* or *in vivo*. In view of the scope of the claimed invention that encompasses various adenoviruses and non-adenoviruses, and the unpredictability of whether said adenoviruses and non-adenoviruses would have a tissue tropism for SMC, increased tropism for endothelial cells, or reduced tissue tropism for liver cells *in vitro* or *in vivo*, one skilled in the art at the time of the invention would no know how to use the claimed invention.

Further, the claims encompass various altered tropism-determining proteins, chimeric proteins, and fragments of virus capsid protein. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life),

and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). It is unclear whether an altered tropism-determining protein, chimeric protein having protein fragments from different viruses could still maintain their specific tropism to a specific cell type as compared to their wild type proteins or any other adenovirus or viruses. Therefore, it would be unpredictable whether various altered tropism-

determining proteins, chimeric proteins having protein fragments from at least two different viruses, such as fragments of virus capsid proteins, could provide a tissue tropism for SMC, increased tropism for endothelial cells, or reduced tissue tropism for liver cells *in vitro* or *in vivo*.

In addition, the specification states "The invention related to the field of molecular genetics and medicine. In particular the present invention relates to the field of **gene therapy**, more in particular to **gene therapy using adenoviruses**" (specification, page 1). Therefore, the claims read on **gene therapy** *in vivo* in light of the specification of the present application. The term "pharmaceutical" in claim 21 also replies therapeutic effects *in vivo*. The specification only discloses adenovirus fiber 16 chimera infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 and none of the disclosed fiber chimeras are targeted specifically to liver and spleen *in vivo*. The specification fails to provide adequate guidance and evidence for the correlation between the claimed recombinant adenovirus encoding a protein of interest and a particular disease in a patient. The specification also fails to provide adequate guidance and evidence for how to deliver the recombinant adenovirus expressing any gene product under the control of any promoter to a patient and sufficient gene products could be produced at the targeted site so as to provide therapeutic effects for a particular disease or disorder in said patient *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be

unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are important factors for a successful gene therapy *in vivo* (e.g. bridging pages 81-

82). In view of such, one skilled in the art at the time of the invention would not know how to use the claimed invention.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require a skilled artisan at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the claims have been amended to read on recombinant adenovirus and the specification provides support for cells that produces a recombinant adenovirus having tropism for smooth muscle cells, the recombinant adenovirus with reduced tissue tropism for liver cells and increased tropism for endothelial cells (amendment, p. 12, last paragraph). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection.

8. Claims 28-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 28-32 recite adenovirus sequences without providing adequate sequence information regarding the genome of the adenovirus claimed. This rejection may be obviated by appropriate deposit of the nucleic acid construct claimed. The declaration by Dr. Jaap Goudsmit

only indicates the deposit of ECACC 96022940 but fails to address deposit of the constructs as claimed in claims 28-32.

The invention consists of adenovirus constructs. Since the constructs are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the construct is not so obtainable or available, the requirements of 35 U.S.C. § 112, regarding "how to make", may be satisfied by a deposit of the constructs. The specification does not disclose a repeatable process to obtain the constructs and it is not apparent if these are readily available to the public. It is noted there is no indication in the specification as to public availability to the claimed constructs. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific construct has been deposited under the Budapest Treaty and that the construct will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 58 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Stevenson et al., 1997 (Journal of Virology, Vol. 71, No. 6, p. 4782-4790).

Claim 58 is directed to a recombinant adenovirus capsid comprising proteins from at least two different adenoviruses and at least a tissue tropism determining fragment is fiber protein of adenovirus subgroup B.

Stevenson teaches preparation of a chimeric fiber cDNA having Ad3 (subgroups B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft incorporated into the genome of an adenovirus vector with E1 and E3 deleted region encoding beta-galactosidase to generate Av9LacZ4, and a recombinant adenoviruses containing the chimeric fiber protein. Stevenson teaches that three cell lines (THP-1, MRC-5, and FaDu) were more efficiently transduced by the vector comprising the Ad3 fiber head than by the Ad5 fiber vector. Stevenson suggests that "exchange of fiber head domain is a viable approach to the production of adenovirus vectors with cell-type specific transduction properties" and may "extend this approach to the use of ligands for a range of different cellular receptors in order to target gene transfer to specific cell types at the level of transduction" (e.g. abstract). Thus, claim 58 is anticipated by Stevenson.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.